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Evaluation Report ERC2014-01

Tea Tree Oil

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Overview

Registration Decision for Compound Tea Tree Oil

Health Canada's Pest Management Regulatory Agency (PMRA), under the authority of the *Pest Control Products Act* and Regulations, has granted conditional registration for the sale and use of Tea Tree Oil Technical and Timorex Gold, containing the technical grade active ingredient tea tree oil, to control powdery mildew on greenhouse pepper, tomato and cucumber, suppress powdery mildew on grape, strawberry and cucurbit vegetables, suppress downy mildew on grape and greenhouse cucumber, and suppress late blight on greenhouse tomato.

An evaluation of available scientific information found that, under the approved conditions of use, the product has value and does not present an unacceptable risk to human health or the environment.

Although the risks and value have been found acceptable when all risk reduction measures are followed, the applicant must submit additional scientific information as a condition of registration.

This Overview describes the key points of the evaluation, while the Science Evaluation section provides detailed technical information on the human health, environmental and value assessments of Tea Tree Oil Technical and Timorex Gold.

What Does Health Canada Consider When Making a Registration Decision?

The key objective of the *Pest Control Products Act* is to prevent unacceptable risks to people and the environment from the use of pest control products. Health or environmental risk is considered acceptable[1] if there is reasonable certainty that no harm to human health, future generations or the environment will result from use or exposure to the product under its proposed conditions of registration. The Act also requires that products have value[2] when used according to the label directions. Conditions of registration may include special precautionary measures on the product label to further reduce risk.

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1 "Acceptable risks" as defined by subsection 2(2) of the *Pest Control Products Act*.

2 "Value" as defined by subsection 2(1) of the *Pest Control Products Act*: "the product's actual or potential contribution to pest management, taking into account its conditions or proposed conditions of registration, and includes the product's (a) efficacy; (b) effect on host organisms in connection with which it is intended to be used; and (c) health, safety and environmental benefits and social and economic impact."

To reach its decisions, the PMRA applies modern, rigorous risk-assessment methods and policies. These methods consider the unique characteristics of sensitive subpopulations in humans (for example, children) as well as organisms in the environment (for example, those most sensitive to environmental contaminants). These methods and policies also consider the nature of the effects observed and the uncertainties when predicting the impact of pesticides. For more information on how the PMRA regulates pesticides, the assessment process and risk-reduction programs, please visit the Pesticides and Pest Management section of Health Canada's website at healthcanada.gc.ca/pmra.

What Is Tea Tree Oil?

Tea tree oil is extracted from a cultivated tea tree native to Australia, New Zealand and Southeast Asia. Tea tree oil contains over 100 components, mostly monoterpenes, sesquiterpenes and their alcohols. As the active ingredient in Timorex Gold, tea tree oil may disrupt cell membrane of the targeted fungal pathogens, though the exact biochemical mode of action is still not fully understood.

Health Considerations

Can Approved Uses of Tea Tree Oil Affect Human Health?

Tea tree oil is unlikely to affect human health when used according to label directions.

Potential exposure to tea tree oil may occur through the diet (food and water) or when handling and applying the end-use product, Timorex Gold, which is proposed as a commercial fungicide for application to various vegetable and fruit crops. When assessing health risks, two key factors are considered: the levels where no health effects occur and the levels to which people may be exposed. The dose levels used to assess risks are established to protect the most sensitive human population (for example, children and nursing mothers). Only uses for which the exposure is well below levels that cause no effects in animal testing are considered acceptable for registration.

Tea tree oil is slightly acutely toxic via the oral route and of low acute toxicity via the dermal and inhalation routes of exposure. It is a severe eye and skin irritant, and is considered to be a skin sensitizer. Although tea tree oil has low acute inhalation toxicity, because of its eye and skin irritancy, it is considered to be a potential respiratory irritant if inhaled. Consequently, the hazard signal words, "CAUTION POISON", "DANGER – EYE AND SKIN IRRITANT", and "POTENTIAL SKIN SENSITIZER" are required on the label.

The acute toxicity of Timorex Gold was low via the oral, dermal, and inhalation routes of exposure. It was moderately irritating to the eyes and skin, and is considered to be a skin sensitizer. Because of its eye and skin irritancy, it is considered to be a potential respiratory irritant if inhaled. As a result, the hazard signal words, "WARNING-EYE AND SKIN IRRITANT" and "POTENTIAL SKIN SENSITIZER" are required on the label.

Residues in Water and Food

Dietary risks from food and water are not of concern.

Timorex Gold is to be applied as a foliar spray using conventional equipment to prevent fungal growth on vegetables and fruit in greenhouses, nurseries, and fields. The major components of tea tree oil (i.e., monoterpenes, sesquiterpenes, and related alcohols) are volatile, and after application, tea tree oil is expected to substantially volatilize with low residence times on plants and soil. In residue trials conducted in Europe, the levels of tea tree oil components on treated crops were less than the limit of quantification 48 hours after the application of Timorex Gold. A preharvest interval of four days is required on the label to further encourage the dissipation of any residues of tea tree oil prior to harvesting treated crops. Also, consumers are exposed to low levels of tea tree oil components in the diet through their use as flavouring substances, in sanitizing solutions for food-processing equipment, and in coatings on food contact surfaces.

Many of the components of tea tree oil have low water solubility, and because of the expected volatilization and low residence time for tea tree oil in environmental media, there is not likely to be any significant contamination of ground or surface water sources of drinking water. In addition, the label directions for Timorex Gold indicate that the product should not be applied directly to water, and that water should not be contaminated when cleaning equipment or disposing of wash water.

Therefore, it is expected that the use of Timorex Gold will not appreciably increase dietary exposure to the components of tea tree oil above existing low background intakes provided that the preharvest interval is observed. Also, it is expected that potential intakes of tea tree oil from drinking water will be negligible. Therefore, the use of Timorex Gold according to label directions is not expected to result in unacceptable dietary or drinking water risks.

Occupational and Bystander Risks from Handling Timorex Gold

Occupational and bystander risks are not of concern when Timorex Gold is used according to label directions, which include protective measures.

There is a potential for dermal and inhalation occupational exposure to tea tree oil during the mixing, loading, and application of Timorex Gold. It is expected that such exposures can be mitigated if workers observe a four hour restricted entry interval (REI) and the precautionary and hygiene statements on the label (for example, wearing of personal protective equipment). In addition, for greenhouse applications, the greenhouse vents should be open and the ventilation fans operating during the REI.

Since Timorex Gold is applied by commercial applicators, potential bystander exposure can be mitigated by following precautionary statements on the label restricting access to the sites of application during mixing, loading, application, and the REI. The product should also not be applied when bystanders are in the vicinity of fields or in areas of greenhouses containing crops to be treated, or present in adjacent structures or buildings where they could be exposed via post-application ventilation from treated greenhouses.

Therefore, occupational exposures to individuals handling Timorex Gold are not expected to result in any unacceptable risks and bystander exposures to the product are expected to be negligible when the product is used according to label directions.

Environmental Considerations

What Happens When Tea Tree Oil Is Introduced Into the Environment?

Tea Tree Oil Technical and its associated end-use product, Timorex Gold, will enter the environment when applied as a fungicide, using field and airblast sprayers, on various field and greenhouse crops. Tea tree oil is composed of several constituents that are all considered to be highly volatile; substantial volatilization is expected within the first 24 hours of application from plant, soil, and water surfaces. Tea tree oil constituents are quickly broken down in air through atmospheric reactions. Because of the short residence time in the environment, exposure to groundwater through leaching and surface waters through runoff is not expected to be significant. A rapid rate of volatilization followed by breakdown in air means that exposure to non-target organisms is expected to be limited. However, acute exposure from direct contact with the spray or spray drift may be possible and was assessed. Based on this, the potential for acute risk to fish, invertebrates, amphibians, and beneficial arthropods was identified. Hazard label statements and mitigative measures are required on the label.

Value Considerations

What Is the Value of Timorex Gold?

Timorex Gold, containing tea tree oil, has demonstrated effectiveness in controlling powdery mildew on greenhouse pepper, tomato and cucumber, suppressing powdery mildew on grape, strawberry and cucurbit vegetables, suppressing downy mildew on grape and greenhouse cucumber, and suppressing late blight on greenhouse tomato. Timorex Gold may be applied before disease development or at the first sign of disease. The multicomponent nature of tea tree oil may greatly reduce the potential for resistance development. Timorex Gold provides a non-conventional option for Canadian growers, especially for organic production.

Measures to Minimize Risk

Labels of registered pesticide products include specific instructions for use. Directions include risk-reduction measures to protect human and environmental health. These directions must be followed by law.

The key risk-reduction measures being proposed on the label of Timorex Gold to address the potential risks identified in this assessment are as follows.

Key Risk-Reduction Measures

Human Health

The signal words, "CAUTION POISON", "DANGER – EYE AND SKIN IRRITANT", "POTENTIAL SKIN SENSITIZER", and "PREVENT ACCESS BY UNAUTHORIZED PERSONNEL" are required on the principal display panel for the technical grade active ingredient label.

The statements, "PREVENT ACCESS BY UNAUTHORIZED PERSONNEL", "Harmful if swallowed. Severely irritating to the eyes, skin and respiratory tract. DO NOT get in eyes, on skin or clothing, or inhale sprays, mists or vapours." are required for the PRECAUTIONS section of the secondary display panel of the technical grade active ingredient.

The signal words, "WARNING–EYE AND SKIN IRRITANT" and "POTENTIAL SKIN SENSITIZER" are required on the principal display panel for the end-use product label.

The following statements are required for the PRECAUTIONS section of the secondary display panel of the end-use product:

"KEEP OUT OF REACH OF CHILDREN", "Causes eye, skin, and mucous membrane irritation. DO NOT get in eyes, on skin or clothing, or inhale, sprays, mists or vapours. Potential skin sensitizer."

"Product contains a petroleum distillate solvent"

"Workers potentially exposed to the product through mixing, loading, application, clean-up and repair activities must wear chemical-resistant goggles or a face shield, a NIOSH/MSHA-approved respirator (R95), long-sleeved shirt and long pants, chemical-resistant gloves and shoes plus socks."

"Keep bystanders out of the areas of the greenhouse to be treated for the duration of the treatment and the restricted entry interval (REI)."

"Do not apply to field crops when bystanders are in the vicinity of the fields to be treated."

"Apply only when the potential for drift to areas of human habitation or areas of human activity such as houses, cottages, schools, and recreational areas is minimal. Take into consideration wind speed, wind direction, temperature inversion, application equipment, and sprayer settings."

The following statements are required for the APPLICATION DIRECTIONS section of the secondary display panel of the end-use product:

"A restricted re-entry interval (REI) of four hours must be observed following application. Do not enter or allow worker entry into treated areas during the REI. For greenhouse applications, vents should be opened and ventilation fans should be operational during the REI."

"Treated crops should not be harvested until a preharvest interval of four days has passed."

Environment

Label statements indicating toxicity to aquatic organisms and beneficial arthropods are required. Buffer zone label statements for the protection of aquatic environments are also required.

What Additional Scientific Information Is Being Requested?

Although the risks and value have been found acceptable when all risk-reduction measures are followed, the applicant must submit additional scientific information as a condition of registration. More details are presented in the Science Evaluation Section of this Evaluation Report or in the Section 12 Notice associated with these conditional registrations. The applicant must submit the following information within the time frames indicated.

Human Health

- All published and unpublished studies of the developmental toxicity of tea tree oil must be submitted by 1 September 2015.

- Information to characterize the metabolic pathways of the major components of tea tree oil and whether residues of the major components and their metabolites are present on treated crops after the application of Timorex Gold must be submitted by 1 September 2015.

Other Information

As these conditional registrations relate to a decision on which the public must be consulted,[3] the PMRA will publish a consultation document when there is a proposed decision on applications to convert the conditional registrations to full registrations or on applications to renew the conditional registrations, whichever occurs first.

The test data cited in this Evaluation Report (i.e. the test data relevant in supporting the registration decision) will be made available for public inspection when the decision is made to convert the conditional registrations to full registrations or to renew the conditional registrations (following public consultation). If more information is required, please contact the PMRA's Pest Management Information Service by phone (1-800-267-6315) or by e-mail (pmra.infoserv@hc-sc.gc.ca).

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[3] As per subsection 28(1) of the *Pest Control Products Act.*

Science Evaluation

Tea Tree Oil

1.0 The Active Ingredient, Its Properties and Uses

1.1 Identity of the Active Ingredient

Active substance	Tea tree oil
Function	Fungicide
Chemical name	
1. International Union of Pure and Applied Chemistry (IUPAC)	Not assigned
2. Chemical Abstracts Service (CAS)	Oils, tea tree
CAS number	68647-73-4
Molecular formula	Not applicable to a mixture
Molecular weight	Not applicable to a mixture
Structural formula	Not applicable to a mixture
Purity of the active ingredient	100.00%

1.2 Physical and Chemical Properties of the Active Ingredient and End-Use Product

Technical Product – Tea Tree Oil Technical

Property	Result
Colour and physical state	Pale yellow liquid
Odour	Characteristic
Melting range	Not applicable as product is a liquid
Boiling point	Estimated as ~200°C
Density	0.885–0.906 g/mL
Vapour pressure	Ranges from 15 to 253 Pa for major components
Ultraviolet (UV)-visible spectrum	Not expected to absorb at $\lambda > 300$ nm
Solubility in water	Ranges from 5 mg/L to 3.3 g/L for major components

Property	Result
Solubility in organic solvents at 20°C	Miscible in 85% ethanol at 0.7
n-Octanol-water partition coefficient (K_{ow})	log K_{ow} ranges from 2.6 to 4.75 for major components
Dissociation constant (pK_a)	Not applicable, as major components are not expected to dissociate at relevant pH
Stability (temperature, metal)	Generally stable to galvanized steel. Exposure to light, heat, air and moisture affect stability and should be avoided.

End-Use Product – Timorex Gold

Property	Result
Colour	Colourless to pale yellow
Odour	Characteristic pungent
Physical state	Liquid
Formulation type	Emulsifiable concentrate
Guarantee	23.80% tea tree oil
Container material and description	Coextruded HDPE 1 L bottles and 5 L cans
Density	0.935 g/mL
pH of 1% dispersion in water	9.00
Oxidizing or reducing action	Not considered to be an oxidizing or reducing agent
Storage stability	Stable for 2 years in HDPE packaging
Corrosion characteristics	Not corrosive to HDPE packaging
Explodability	Not likely to be explosive

1.3 Directions for Use

Timorex Gold is for use on various vegetable and fruit crops at the rate of 0.5–1.0%. Timorex Gold may be applied in the early stages of disease infestation for initial control in the greenhouse, nursery or field using conventional equipment as a foliar spray. Good coverage and wetting of the foliage is required. Early treatment prevents diseases from developing. Reapply throughout the growing season at 7–14 day intervals. Use the shorter application interval and higher rate under conditions that promote rapid disease development.

1.4 Mode of Action

Tea tree oil contains over 100 components, mostly monoterpenes, sesquiterpenes and their alcohols. The mode of action for tea tree oil is mainly through membrane disruption of the targeted micro-organisms; however, the exact biochemical mode of action is still under investigation. It is believed that the multicomponent nature of tea tree oil may greatly reduce the potential for resistance development. Tea tree oil is used as a preventative treatment against the various stages of fungal growth.

2.0 Methods of Analysis

2.1 Methods for Analysis of the Active Ingredient

The method provided for the analysis of the active ingredient components in Tea Tree Oil Technical has been validated and assessed to be acceptable for the determinations.

2.2 Method for Formulation Analysis

The method provided for the analysis of the active ingredient components in the formulation has been validated and assessed to be acceptable for use as an enforcement analytical method.

3.0 Impact on Human and Animal Health

3.1 Toxicology Summary

A detailed review of the toxicological database for tea tree oil, consisting of toxicity studies and waiver rationales, was conducted. The scientific quality of the data is acceptable and the database is considered sufficiently complete to define the majority of the toxic effects that may result from exposure to tea tree oil.

The applicant submitted acute oral, dermal, and inhalation toxicity, irritation (eye and skin), sensitization, short-term toxicity (oral), and mutagenicity studies on tea tree oil. A data waiver rationale was submitted requesting that the short-term inhalation toxicity data requirements be addressed based on information from the submitted short-term oral toxicity study combined with a consideration of potential inhalation exposure. Similarly, a data waiver rationale was submitted requesting that the developmental toxicity information requirements be addressed by information from a published study of the developmental toxicity of a component of tea tree oil, α-terpinene, combined with published information illustrating the similarity of the metabolism of the main components of tea tree oil. The applicant also submitted acute oral, dermal and inhalation toxicity, irritation (eye and skin), and sensitization studies on Timorex Gold.

Tea tree oil is slightly acutely toxic via the oral route of exposure and of low toxicity via the dermal and inhalation routes. It is a severe skin irritant, and it is considered to be a severe eye irritant and a skin sensitizer. Because it is a severe eye and skin irritant, tea tree oil has the potential to cause respiratory irritation if inhaled. Timorex Gold is of low acute toxicity via the oral, dermal, and inhalation routes of exposure. It is moderately irritating to the eyes and skin, and it is a skin sensitizer. Because it is moderately irritating to the eyes and skin, Timorex Gold has the potential to cause respiratory irritation if inhaled.

A 90-day oral toxicity study in rats was submitted for tea tree oil. The lowest observed adverse effect level (LOAEL) was determined to be 60 mg/kg bw/day for males and 120 mg/kg bw/day for females. For males, the LOAEL was based on testicular toxicity (i.e., reduced sperm counts and motility) progressing to sperm abnormalities and microscopic changes in the testes and epididymides at 120 mg/kg bw/day. For females the LOAEL was based on mortality, and the no observed adverse effect levels (NOAELs) for males and females were 30 mg/kg bw/day and 60 mg/kg bw/day, respectively.

A data waiver rationale was submitted in lieu of a 90-day inhalation toxicity study for tea tree oil. The rationale was based on the expectation that repeated inhalation exposures to significant levels of airborne tea tree oil are unlikely to occur given the use pattern of the end-use product, tea tree oil has low acute toxicity via inhalation, and 90-day inhalation exposures to tea tree oil are likely to produce similar effects as were observed in the 90-day oral toxicity study. The PMRA accepted this rationale provided that precautionary statements including the use of personal protective equipment to prevent repeated occupational inhalation exposures are included on the label for the end-use product.

In the submitted data waiver rationale for the developmental toxicity information requirements, the applicant noted that based on published studies, the major components of tea tree oil including α-terpinene are structurally similar and most are metabolized to polar compounds and/or conjugated and excreted in the urine. Also, α-terpinene and the component present in the greatest concentration, terpinen-4-ol, can be synthesized from the same parent compound, both compounds can be metabolized by similar pathways in mammals, and α-terpinene can also undergo epoxidation at the 3,4-ring position to produce terpinen-4-ol and terpinen-3-ol. Consequently, the developmental toxicity of α-terpinene can be considered to be representative of the potential developmental toxicity of terpinen-4-ol and the other major terpinoid components of tea tree oil. While there are uncertainties associated with extrapolating the effects observed for α-terpinene to the whole oil, this data waiver rationale was accepted by the PMRA on the condition that the registrant will provide all published and unpublished studies of the developmental toxicity of tea tree oil. In the submitted published study of the prenatal developmental toxicity of α-terpinene administered to rats by gavage during gestation, a LOAEL of 125 mg/kg bw/day was identified for maternal toxicity based on decreased body weight gain. A LOAEL of 60 mg/kg bw/day was identified for developmental toxicity based on increased incidences of retarded ossification and irregularly shaped os squamosum, with increased incidences of delayed and incomplete ossification of the skull and/or ribs reported at 125 and 250 mg/kg bw/day and decreased fetal body weights, decreased thymus weights, increased kidney weights, and increased incidences of extra cervical ribs observed at 250 mg/kg bw/day.

The NOAELs for maternal and developmental toxicity were 60 and 30 mg/kg bw/day, respectively.

Tea tree oil was not mutagenic when tested in a reverse mutation assay conducted in multiple strains of *Salmonella typhimurium*. It also gave negative results in an in vivo mouse bone marrow micronucleus assay.

Results of the toxicology studies conducted on laboratory animals with Timorex Gold and tea tree oil are summarized in Appendix I, Tables 1 and 2.

3.2 Incident Reports

Since 26 April 2007, registrants have been required by law to report incidents, including adverse effects to health and the environment, to the PMRA within a set time frame. Information on the reporting of incidents can be found on the Pesticides and Pest Management portion of Health Canada's website at healthcanada.gc.ca/pmra. Incidents from Canada and the United States were searched and reviewed for tea tree oil.

As of 4 June 2012, there was one incident report submitted to the PMRA associated with tea tree oil, which was not registered as an active ingredient in Canada. A dog was given a topical flea and tick treatment and a bath in an unknown concentration of tea tree oil for an unknown duration. The dog owner also treated the home in which the dog resided with insecticides. Although the dog experienced respiratory, neurological, and gastrointestinal effects, the self-reported description and details of the incident are vague, so it is not possible to determine whether the observed effects are causally related to the dog's exposure to tea tree oil or any of the other products used.

No incidents associated with products containing tea tree oil have been reported to the United States Environmental Protection Agency or to the California Department of Pesticide Regulation Pesticide Illness Surveillance Program.

3.3 Occupational and Residential Risk Assessment

3.3.1 Mixer, Loader and Applicator Exposure and Risk Assessment

Occupational exposure to tea tree oil in Timorex Gold is expected to be by the dermal and inhalation routes of exposure during mixing, loading, and application. To limit occupational exposure during these activities, personal protective equipment is required including chemical-resistant goggles or a face shield, a NIOSH/MSHA-approved respirator, a long-sleeved shirt and long pants, chemical-resistant gloves, and shoes plus socks. Other precautionary and hygiene statements on the label require the user to avoid breathing vapours, sprays or mists and avoid contact with skin, eyes or clothing. Users should also wash thoroughly with soap and water after handling, and remove and wash contaminated clothing before reuse. Therefore, when mixers, loaders, and applicators follow the label instructions for Timorex Gold, occupational exposures to tea tree oil are not expected to result in any unacceptable risks.

3.3.2 Bystander Exposure

Since Timorex Gold is a commercial product, potential exposure to bystanders can be mitigated by restricting access to the sites of application during mixing, loading, application, and the restricted-entry interval (REI). The end-use product should not be applied when bystanders are in the near vicinity of fields containing crops to be treated. Also, Timorex Gold should not be applied when bystanders are present in areas of greenhouses to be treated or in adjacent structures or buildings where they could be exposed via postapplication ventilation of treated greenhouses. Bystander exposure is expected to be negligible following the application of these mitigation measures.

3.3.3 Postapplication Exposure

Postapplication activities are expected to follow typical agricultural practices for the greenhouse and field crops to which Timorex Gold will be applied. To limit postapplication exposures, an REI of four hours must be followed, and for greenhouse applications, the vents should be open with ventilation fans running during the REI. When label directions for Timorex Gold are followed including adherence to the REI and ventilation of greenhouses, postapplication exposures to tea tree oil are not expected to result in any unacceptable risks.

3.4 Food Residues Exposure Assessment

3.4.1 Food and Drinking Water

Two European trials were conducted to determine the residues of tea tree oil on green peppers, tomatoes, and cucumbers in greenhouses following single applications of either Timorex Gold (i.e., 23.8% tea tree oil) or a high concentration formulation (i.e., 66% tea tree oil). Tea tree oil residues were measured via GC/MS analysis of three tea tree oil components, terpinen-4-ol, γ-terpinene, and 1,8-cineole with a level of quantification (LOQ) of 0.05 mg/kg. In the first study, when Timorex Gold was applied to tomatoes and peppers at rates similar to the proposed Canadian rates (i.e., 1.19 to 3.57 kg a.i./ha), all three components of tea tree oil were less than the LOQ when measured at times starting from immediately after application up to and including 48 hours later. When the high concentration formulation (i.e., 66% tea tree oil) was applied to crops at application rates in excess of the proposed Canadian rates (i.e., maximum of 13.20 kg a.i./ha on peppers), residues of terpinen-4-ol as high as 0.36 mg/kg were measured immediately after application to peppers, decreasing to 0.10 mg/kg 24 hours later. At 48 hours after application of the high concentration formulation, terpinen-4-ol levels were less than the LOQ. Residues of the other tea tree oil components were all less than the LOQ, at all times, and on all crops after application of the high concentration formulation. In the second study, only Timorex Gold was applied to tomatoes, green peppers, and cucumbers at rates similar to the proposed Canadian rates and the residues of all tea tree oil components were less than the LOQ when measured immediately after application up to 48 hours later.

The major components of tea tree oil are approved by the United States Food and Drug Administration for use as food flavouring substances, in sanitizing solutions for food equipment and utensils, and in coatings for food contact surfaces. Also, the major components of tea tree oil are moderately or highly volatile and in a submitted published study, 98% of a 7.4 mg/cm^2 sample of tea tree oil applied to filter paper evaporated after four hours at a temperature of 30 °C. For greenhouse applications of Timorex Gold, it is recommended that the greenhouse vents be opened with the ventilation fans turned on during the four hour restricted entry interval to further enhance the evaporation of any tea tree oil residues. Finally, it is recommended that a preharvest interval of four days be observed to reduce the residue levels.

Apart from terpinen-4-ol, most of the major components of tea tree oil have low water solubility and moderate octanol-water partition coefficients (LogK_{ow}). In addition, the label instructions for Timorex Gold indicate that the product should not be applied directly to water, to areas where surface water is present, or to intertidal areas below the mean highwater mark. Also, water should not be contaminated when cleaning application equipment or disposing of washwater. Given the water solubility, the LogK_{ow} values, and the moderate to high volatility of most of the major components of tea tree oil, and the label instructions regarding procedures for avoiding the contamination of water, it is likely that any contamination of surface or groundwater sources of drinking water from the use of Timorex Gold would be negligible.

Therefore, the use of Timorex Gold is not expected to result in significant food residues of tea tree oil components, increase dietary intakes of tea tree oil components above existing background levels, and result in any unacceptable dietary risks when the product is used according to label instructions including observing a preharvest interval of four days. On the other hand, as the residue studies did not measure α-terpinene and the submitted published study of the prenatal developmental toxicity of α-terpinene administered to rats by gavage during gestation identified developmental toxicity effects, another condition of registration is the submission of information to characterize the metabolic pathways of the major components of tea tree oil and whether residues of the major components and their metabolites are present on treated crops after the application of Timorex Gold.

Methyleugenol is a naturally occurring substance found in spices, herbs, fruit, and essential oils. As discussed in the PMRA document *Re-evaluation of Citronella Oil and Related Active Compounds for Use as Personal Insect Repellents* (PACR2004-36), "methyleugenol has been demonstrated to be mutagenic, to induce tumour formation in rats and mice, and is reasonably anticipated to be a human carcinogen". In response to a request for information on the levels of methyeugenol in the technical grade active ingredient, the applicant submitted a dietary risk assessment of methyleugenol from the application of Timorex Gold to food crops including an analysis of the concentration of the compound in the technical grade active ingredient. The resulting screening level estimates of methyleugenol intake for children and adults were determined to be less than potential exposures from personal insect repellents containing methyleugenol at the PMRA established limit (0.0002%). Methyleugenol intakes estimated by the applicant are also within published estimates of background dietary intakes from flavourings, spices and other sources. Consequently, it is not expected that the use of Timorex Gold on vegetables and fruit will result in dietary intakes of methyleugenol greater than existing background dietary intakes.

3.4.2 Maximum Residue Limits (MRLs)

As part of the assessment process prior to the registration of a pesticide, Health Canada must determine that the consumption of the maximum amount of residues that are expected to remain on food products when a pesticide is used according to label directions will not be a concern to human health. This maximum amount of residues expected is then legally established as a MRL under the *Pest Control Products Act* for the purposes of the adulteration provision of the *Food and Drugs Act*. Health Canada sets science-based MRLs to ensure the food that Canadians eat is safe.

In European residue trials using application rates for Timorex Gold comparable to the proposed Canadian application rates, residues of tea tree oil components on treated vegetables were less than the LOQ for the analytical method at all times. Application rates greater than proposed Canadian rates based on the use of a high concentration formulation (i.e., 66% tea tree oil) on green peppers resulted in quantifiable residues up to 24 hours after application, but residues were less than the LOQ after 48 hours. In addition, the major components of tea tree oil are volatile and have been approved for use as food flavouring agents, in sanitizing solutions for food-processing equipment and utensils, and in coatings on food contact surfaces by the United States Food and Drug Administration. Consequently, the proposed use of Timorex Gold as a fungicide on selected vegetable and fruit crops, including a preharvest interval of four days, is not expected to significantly increase dietary exposure to tea tree oil components beyond levels currently in the diet and the PMRA has not required the establishment of a MRL for tea tree oil.

4.0 Impact on the Environment

4.1 Fate and Behaviour in the Environment

All of the major tea tree oil constituents are considered to be volatile substances. Vapour pressures are all >0.01 Pa, and substantial volatilization may be expected within the first 24 hours of application from plant and soil surfaces. All of the major tea tree oil constituents are also expected to volatilize from water surfaces. Based on the high volatility of the different tea tree oil constituents, it is expected that their residence time on plants, soil, and surface water is low. In addition, because of the low residence time on these environmental media, exposure to groundwater through leaching and surface waters through runoff is not expected to occur in any significant way. The fast dissipation from the different environmental compartments limits the extent of other environmental processes occurring (such as biodegradation). Submitted laboratory studies and other information have, however, indicated that any residues of tea tree oil or its constituents contacting microbially active media will be rapidly degraded/metabolized. In air, components of tea tree oil readily react with ozone, and nitrate and hydroxyl radicals; reactions can occur on the order of minutes to hours. Therefore, tea tree oil is not expected to persist in the environment.

4.2 Environmental Risk Characterization

Tea tree oil was assessed for its potential to cause acute risk to non-target organisms, as acute exposure could occur from spray drift or a direct spray.

The environmental risk assessment integrates the environmental exposure and ecotoxicology information to estimate the potential for adverse effects on non-target species. This integration is achieved by comparing exposure concentrations with concentrations at which adverse effects occur. Estimated environmental concentrations (EECs) are concentrations of pesticide in various environmental media, such as food, water, soil and air. The EECs are calculated by using standard methods which take into consideration the application rate(s), chemical and environmental fate properties, including the dissipation of the pesticide between applications. Ecotoxicology information includes acute and chronic toxicity data for various organisms or groups of organisms from both terrestrial and aquatic habitats including invertebrates, vertebrates, and plants. Toxicity endpoints used in risk assessments may be modified to account for potential differences in species sensitivity as well as varying protection goals (i.e. protection at the community, population, or individual level).

Initially, a screening level risk assessment is performed to identify pesticides and/or specific uses that do not pose a risk to non-target organisms, and to identify those groups of organisms for which there may be a potential risk. The screening level risk assessment uses simple methods, conservative exposure scenarios (for example, direct application at a maximum cumulative application rate) and sensitive toxicity endpoints. A risk quotient (RQ) is calculated by dividing the exposure estimate by an appropriate toxicity value (RQ = exposure/toxicity), and the risk quotient is then compared to the level of concern (LOC). If the screening level RQ is below the LOC, the risk is considered negligible and no further risk characterization is necessary. If the screening level RQ is equal to or greater than the LOC, then a refined risk assessment is performed to further characterize the risk. A refined assessment takes into consideration more realistic exposure scenarios (such as drift to non-target habitats) and might consider different toxicity endpoints. Refinements may include further characterization of risk based on exposure modelling, monitoring data, results from field or mesocosm studies, and probabilistic risk assessment methods. Refinements to the risk assessment may continue until the risk is adequately characterized or no further refinements are possible.

4.2.1 Risks to Terrestrial Organisms

A screening level risk assessment indicated potential acute risk to predatory arthropods and parasitic arthropods (RQ's >2.0), small, medium, and large size birds for several food guilds, and medium and large sized herbivorous mammals (RQ's >1.0) (Appendix I, Table 3). The LOC for bees was not exceeded.

A refined risk assessment considering in-field and off-field exposure was conducted for predatory and parasitic arthropods. Under the proposed use pattern, application on crops will occur during periods of full leaf. As such, a three-dimensional foliar deposition scenario was considered for this refinement, where a certain fraction of the spray deposit is intercepted by the crop (in-field exposure) or the vegetation adjacent to the treated area (off-field exposure). For the in-field exposure, the cumulative application rate (Appendix I, Table 3) is multiplied by a harmonized foliar deposition fraction (F_{int}) for various crops to determine an in-field EEC. For Timorex Gold, the highest application rate is on grapes; this crop corresponds to an F_{int} of 0.8 (assuming full leaf development phase of growth). With a cumulative application rate of 4.485 kg a.i./ha, the foliar in-field EEC is, therefore, 3588 g a.i./ha. The resulting in-field RQs are <3.73 (predatory arthropod) and <15 (parasitic arthropod) (Appendix I, Table 4). The refined off-field EEC for predatory and parasitic arthropods is determined by multiplying the screening level off-field EEC by a vegetation distribution factor of 0.1. For the current case, the screening level off-field EEC is the maximum cumulative application rate of 4.485 kg a.i./ha x a drift factor of 0.74 (for early air blast, the highest drift factor for the use pattern), or 3.319 kg a.i./ha. Therefore, the refined off-field EEC equals 332 g a.i./ha, which results in RQs of <0.4 (predatory arthropod) and <1.4 (parasitic arthropods) (Appendix I, Table 5). Since some risk was observed for predatory and parasitic arthropods at the refined level for both in- and off-field locations, a label statement indicating toxicity and minimizing drift is required.

Further characterization of risk was conducted for birds and mammals where the screening level assessment indicated that the LOC was exceeded. The characterization reviewed the potential for risk for all food guilds using maximum and mean residue EEC values for both in-field and off-field scenarios. The maximum levels represent a worst case scenario, while the mean EECs are used to represent more realistic levels under the proposed use pattern. Using maximum levels for in-field exposure, RQs ranging from 1.1 to 4.8 were observed for various animal sizes and food guilds (Appendix I, Table 4). The off-field RQs using maximum residues ranged from 1.0 to 2.9 and, generally, exceeded the LOC less frequently than for in-field exposures (Appendix I, Table 5). Using mean residues, no RQs exceeded the LOC of 1.0 for mammals, and were slightly above 1.0 only for certain bird sizes and food guilds (Appendix I, Table 6). When considering an off-field scenario using mean residue levels, small and medium birds that consume small insects, and large birds consuming short grass, were at risk and were only slightly higher than 1.0 (Appendix I, Table 7). In general, the RQ values for all further characterization scenarios did not greatly exceed 1.0.

Considering this, and considering that due to the volatility of the active ingredient the residence time on food items consumed by birds and mammals will be short, the risk to birds and mammals through the use of tea tree oil is expected to be negligible under the proposed use pattern.

4.2.2 Risks to Aquatic Organisms

A screening level risk assessment indicated potential acute risk to freshwater aquatic invertebrates, fish, and amphibians (RQ's >1.0) (Appendix I, Table 3). A refined risk assessment was, therefore, conducted for these groups.

The refined risk assessment considered the attenuation of pesticide deposition on aquatic environments with increased distance from the treatment site. Based on this, some RQ values exceeded the LOC, and buffer zones for aquatic habitats were calculated. Based on the EEC for 80 cm (invertebrates and fish) and 15 cm (amphibians, using a fish endpoint surrogate), buffer zones ranged from 1 metre to 20 metres, depending on either the crop, application method, stage of crop growth at time of application, and whether considering freshwater or marine habitat.

Ecoscenarios for groundwater and runoff were not considered for tea tree oil. Based on the high volatility of the individual components of tea tree oil (vapor pressure range 14.9 to 544 Pa), substantial volatilization is expected within the first 24 hours of application from plant, soil, and water surfaces. Because of the short residence time on these environmental media, exposure to ground water through leaching and surface water through runoff is not expected to be significant.

5.0 Value

5.1 Effectiveness Against Pests

5.1.1 Acceptable Efficacy Claims

5.1.1.1 Control of Powdery Mildew on Greenhouse Tomato, Pepper and Cucumber

Results from six greenhouse trials on tomato conducted in Israel and Poland in 2007 were reviewed. Powdery mildew pressure was generally low to moderate (4 – 50% disease incidence) across all six trials. Three powdery mildew pathogens *Oidium neolycopersici, O. lycopersici* and *Leveillula taurica* were tested. Overall, the disease control provided by Timorex Gold ranged from 75% to 100% for rates of 0.5% and 1.0% (an average of 90%). Numerically higher disease control was achieved at the rate of 1.0% compared to 0.5% rate. The efficacy was superior to Serenade Max (Registration Number 28549) compared in three trials. The claim for control of powdery mildew on greenhouse tomato is supported at the rates of 0.5–1.0%.

Results from four greenhouse trials on pepper conducted in Israel in 2006 and 2008 were reviewed. Powdery mildew pressure was low to moderate (12 – 62% disease incidence) across four trials. The disease control provided by Timorex Gold ranged from 72% to 98% (averaged 89% control based on disease severity rating) for rates of 0.4–0.8%. The performance of Timorex Gold was the same under low disease pressures (12–24%) compared to moderate disease pressures (62%). The rate of 0.8% was used in two trials and consistently provided better disease control than the lower rates. There was no registered commercial standard included in these trials. In addition, evidence from the greenhouse tomato trials indicated that Timorex Gold provided good control on the same powdery mildew pathogen at rates of 0.5–1.0%. The claim for control of powdery mildew on greenhouse pepper is supported at the rates of 0.5–1.0%.

Results from six greenhouse trials on cucumber conducted in Israel, Latvia and Poland in 2006–2008 were reviewed. Powdery mildew pressure was low to moderate (17–62% disease incidence) across six trials. Two powdery mildew pathogens *Sphaerotheca fuliginea* and *Erysiphe cichoracearum* were tested. Under low disease pressures (averaged 32% in four trials), Timorex Gold provided good disease control of 90% at the rates of 0.5% and 1.0%. Under moderate disease pressures (averaged 58% in two trials), Timorex Gold provided 71% disease control at rates ranging between 0.5% and 1.0%. The high rate (1.0%) treatment generally achieved better disease control than the treatments with lower rates. Six additional greenhouse trials on cucumber conducted in France, Germany, Netherlands, Israel and the UK in 2009 and Spain in 2008 were also provided and reviewed. Disease pressure was varied from 5% up to 92%. Timorex Gold consistently provided powdery mildew control of 89% (79–98%) at 0.5% and 94% (85–100%) at 1.0% across all six trials. The claim for control of powdery mildew on greenhouse cucumber is supported at the rates of 0.5–1.0%.

5.1.1.2 Suppression of Late Blight on Greenhouse Tomato

Results from two greenhouse trials conducted in Poland in 2007 were reviewed. Late blight pressure was moderate to high (35–70% disease incidence) across two trials. Timorex Gold provided disease control of 38% to 57% with numerically lower control observed at the rate of 0.5% than at the rate of 1.0%. The performance of Timorex Gold was better under low disease pressures (35%) compared to high disease pressures (70%), with average disease control of 48% and 43%, respectively. As supplementary data, the result from one greenhouse potato trial on late blight was also reviewed for this claim. The trial was conducted in Israel in 2007. Late blight pressure was low (9%) in the trial. Timorex Gold treatment achieved 64–84% disease control. The claim for suppression of late blight on greenhouse tomato is supported at the rates of 0.5-1.0%.

5.1.1.3 Suppression of Downy Mildew on Grape and Greenhouse Cucumber

Results from three trials on grape, including one greenhouse and two field trials, were reviewed. Two trials were conducted in India (field) and Italy (greenhouse) in 2007, and one field trial was conducted in Ontario in 2008. Downy mildew pressure in three trials ranged from low to high (23% to 68%). Timorex Gold reduced downy mildew severity by 50% under 23% disease pressure and by 94% under 67% disease pressure in field trials. In the greenhouse, 70% of downy mildew control was achieved with Timorex Gold treatment under disease pressure of 68%. Timorex Gold at a rate of 0.75% was tested in the Ontario trial; however, it was less effective than either the commercial standard (Captan) or the lower rate of Timorex Gold (0.5%). Considering the inconsistent result from the rate of 0.7% and lack of data support for higher rate in the rate range proposed, the claim for suppression of downy mildew on grape at the rate of 0.5–1.0% is supported with conditions, pending additional confirmatory value evidence.

Results from five greenhouse trials on cucumber conducted in Poland, Netherlands, Greece and Germany in 2007 and 2009 were reviewed. Under low downy mildew pressure (8–12% in two trials), Timorex Gold provided 64–88% (averaged 75%) disease control compared to the non-treated control at the rate range from 0.5% to 1.0%. Under high disease pressure (64–96%) in two trials conducted in Poland, Timorex Gold provided 42–90% (averaged 66%) of disease control at the rate range from 0.5% to 1.0%. However, Timorex Gold only achieved less than 30% of downy mildew control in one trial conducted in Netherlands with 35% of downy mildew infection in the non-treated control. The rate of 1.0% consistently provided better disease control than the lower rates applied in same trials. The claim for suppression of downy mildew on greenhouse cucumber is supported at the rates of 0.5–1.0%.

5.1.1.4 Suppression of powdery mildew on cucurbit vegetables, grape and strawberry

Result from nine trials (two greenhouse and seven field trials) on zucchini, squash, watermelon and pumpkin conducted in the United States (California), Israel and Mexico in 2006–2009 were reviewed. Powdery mildew pressure was high (80–90%) in two pumpkin field trials. Timorex Gold at the rate of 0.5% provided 64–73% control compared to the non-treated controls in the pumpkin trials. Powdery mildew pressure was high (68–80%) in two zucchini trials in greenhouse and low to high (9–80%) in four field trials on zucchini, squash and watermelon. In greenhouse zucchini trials, Timorex Gold provided good disease control (81–96%) at all rates (0.4–1.0%) applied. In field trials across all vegetable species, Timorex Gold provided 74% control under low disease pressures (averaged 21% from three trials) and 40–73% control under high disease pressures (56–69% in two trials) at the rates of 0.5–1.0%. Based on the value information, the claim for suppression of powdery mildew on cucurbit vegetables at the rate of 0.5–1.0% is supported with conditions, pending additional confirmatory value evidence.

Results from eight field trials on grape conducted in Canada, US, India, Turkey, Israel and South Africa in 2006–2008 were reviewed. In one trial conducted in Canada, Timorex Gold reduced powdery mildew by 94% under moderate mildew pressure (39%) at the rate of 0.5%. In one trial conducted in California, Timorex Gold reduced powdery mildew by 56–66% under relatively high mildew pressure (64%) at the rate of 0.5–0.75%. Six other trials were conducted in India, Turkey, Israel and South Africa. Powdery mildew pressure was moderate to high (26–100%) across all trials. Timorex Gold reduced powdery mildew by 86% under moderate mildew pressure (26–36% in two trials) and 70% under high mildew pressure (averaged 85% from four trials) at the rate between 0.5% and 1.0%. The disease control on fruits (disease severity on bunches) reached 75% (56–93%) and 80% (62–95%) in all trials for rates of 0.5% and 1.0%, respectively. The claim for suppression, rather than control, of powdery mildew on grape is supported at the rates of 0.5–1.0%.

Results from four field trials conducted in Israel and Argentina in 2008 and 2009 were reviewed. Powdery mildew pressure was high (60 – 75%) across four trials. The powdery mildew control provided by Timorex Gold ranged from 45% to 83% (averaged 67%) for rates of 0.5–1.0%. Since the field trials were conducted outside Canada, the registrant provided climate diagrams from Israel and Argentina to demonstrate comparable climatic conditions (temperature and humidity) to the key strawberry growing regions in Canada (Ontario/Quebec and British Columbia). The claim for suppression, rather than control, of powdery mildew on strawberry is supported at the rates of 0.5–1.0%.

5.2 Phytotoxicity to Host Plants

Phytotoxicity was reported in three trials, including one tomato trial and one cucumber trial from Latvia, and one grape trial from South Africa. Small necrotic spots appeared on some leaves on tomato and cucumber trials in Latvia; however, the tomato or cucumber yield was not affected by the leaf damage. The leaf spots were due to incorrect application in these trials. In the grape trial, Timorex Gold at the higher rate (1.0%) caused unacceptable phytotoxicity symptoms on the berries with golden brown spots. The symptoms were dosage related. A rationale states that a highly sensitive grape variety was used in this case. A warning statement has been included in the Timorex Gold label.

5.3 Economics

No market analysis was done for this application.

5.4 Sustainability

5.4.1 Survey of Alternatives

Refer to Appendix I, Table 8 for a summary of the active ingredients currently registered for the same uses as Timorex Gold.

5.4.2 Compatibility with Current Management Practices Including Integrated Pest Management

The use of Timorex Gold is compatible with current integrated pest management practices and production practices.

5.4.3 Information on the Occurrence or Possible Occurrence of the Development of Resistance

Due to the specific mode of action and the multicomponent nature of tea tree oil for Timorex Gold, resistance management is not a concern at this time.

5.4.4 Contribution to Risk Reduction and Sustainability

Timorex Gold offers a new mode of action to Canadian growers for use on labelled diseases and crops. The use of Timorex Gold will contribute to the integrated pest management practices for labelled crops.

6.0 Pest Control Product Policy Considerations

6.1 Toxic Substances Management Policy Considerations

The Toxic Substances Management Policy (TSMP) is a federal government policy developed to provide direction on the management of substances of concern that are released into the environment. The TSMP calls for virtual elimination of Track 1 substances [those that meet all four criteria outlined in the policy, i.e., persistent (in air, soil, water and/or sediment), bio-accumulative, primarily a result of human activity and toxic as defined by the *Canadian Environmental Protection Act*].

Tea Tree Oil Technical and the end-use product, Timorex Gold, were assessed in accordance with the PMRA Regulatory Directive DIR99-03[4]:

- Tea tree oil does not meet the Track 1 criteria as the active ingredient is not highly toxic, and is not expected to be persistent in the environment or to bioaccumulate.

- There are also no formulants, contaminants or impurities present in the end-use product, Timorex Gold that would meet the TSMP Track 1 criteria.

[4] Regulatory Directive DIR99-03, *The Pest Management Regulatory Agency's Strategy for Implementing the Toxic Substances Management Policy.*

6.2 Formulants and Contaminants of Health or Environmental Concern

During the review process, contaminants in the technical and formulants and contaminants in the end-use product are compared against the *List of Pest Control Product Formulants and Contaminants of Health or Environmental Concern* maintained in the *Canada Gazette*.[5] The list is used as described in the PMRA Notice of Intent NOI2005-01[6] and is based on existing policies and regulations including DIR99-03 and DIR2006-02,[7] and taking into consideration the Ozone-depleting Substances Regulations, 1998, of the *Canadian Environmental Protection Act* (substances designated under the Montreal Protocol). The PMRA has reached the following conclusions:

- Tea Tree Oil Technical and the end-use product, Timorex Gold do not contain any formulants or contaminants of health or environmental concern identified in the *Canada Gazette*.

The use of formulants in registered pest control products is assessed on an ongoing basis through PMRA formulant initiatives and Regulatory Directive DIR2006-02.

7.0 Summary

7.1 Human Health and Safety

The submitted toxicology database is sufficiently complete to define the majority of toxic effects that may result from exposure to tea tree oil. Tea tree oil is slightly acutely toxic via the oral route and of low acute toxicity via the dermal and inhalation routes of exposure. It is a severe skin irritant and is considered to be a severe eye irritant and a skin sensitizer. Because of its severe eye and skin irritancy, tea tree oil is considered to be a potential respiratory irritant if inhaled. The end-use product Timorex Gold is of low toxicity via the oral, dermal, and inhalation routes of exposure. It is moderately irritating to the eyes and skin and is considered to be a skin sensitizer. Because of its irritancy to eyes and skin, Timorex Gold is considered to be a potential respiratory irritant if inhaled.

While the PMRA has considered the developmental toxicity of α-terpinene to be representative of the potential developmental toxicity of terpinen-4-ol and the other major terpinoid components of tea tree oil, there are uncertainties associated with extrapolating the effects observed for α-terpinene to the whole oil. Therefore, all published and unpublished studies of the developmental toxicity of tea tree oil must be submitted as a condition of registration.

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5 *Canada Gazette*, Part II, Volume 139, Number 24, SI/2005-114 (2005-11-30) pages 2641-2643: *List of Pest Control Product Formulants and Contaminants of Health and Environmental Concern* and in the order amending this list in the *Canada Gazette*, Part II, Volume 142, Number 13, SI/2008-67 (2008-06-25) pages 1611-1613. *Part 1 Formulants of Health or Environmental Concern, Part 2 Formulants of Health or Environmental Concern that are Allergens Known to Cause Anaphylactic-Type Reactions and Part 3 Contaminants of Health or Environmental Concern.*

6 NOI2005-01, *List of Pest Control Product Formulants and Contaminants of Health or Environmental Concern under the New Pest Control Products Act.*

7 DIR2006-02, *Formulants Policy and Implementation Guidance Document.*

Occupational exposures to tea tree oil are expected to be minimal if the precautionary statements and recommended personal protective equipment on the product label are followed. Bystander exposure is likely to be negligible. Postapplication exposure can be minimized by following the precautionary statements on the label, and by observing the REI.

While dietary exposure to tea tree oil from the use of Timorex Gold on food crops is not expected to result in unacceptable dietary risks when the product is used according to label instructions including observing the preharvest interval, the residue studies did not measure α-terpinene. Given that the submitted published study of the prenatal developmental toxicity of α-terpinene administered to rats by gavage during gestation identified developmental toxicity effects, information to characterize the metabolic pathways of the major components of tea tree oil and whether residues of the major components and their metabolites are present on treated crops after the application of Timorex Gold must be submitted as a condition of registration. An MRL was not required for tea tree oil.

7.2 Environmental Risk

Tea tree oil and the associated end-use product Timorex Gold are composed of highly volatile substances that will dissipate rapidly from all environmental media once applied. Due to this rapid volatilization from environmental media, exposure to most non-target organisms is expected to be minimal through the use pattern. It was, however, considered that acute exposures could occur (through direct exposure to the treatment spray or spray drift) and based on the risk assessment, some potential for acute risk towards beneficial arthropods, fish, and amphibians was identified. As a result, mitigative label statements indicating tea tree oil toxicity towards these organisms, and statements outlining buffer zones for the protection of aquatic habitats, are required.

7.3 Value

Value information was provided to support the use of Timorex Gold to control or suppress the labeled diseases on various crops. Confirmatory evidence is required to confirm the consistency of product performance on two crop/disease combinations. Timorex Gold has been identified in the Canadian Grower Priority Database (CGPD) as intermediate priorities for powdery mildew on grape and greenhouse cucumber, and downy mildew on grape. The product offers an additional tool for Canadian organic growers for disease and resistance management.

A summary of the proposed and accepted/ conditionally accepted uses for these end use products is presented in Appendix I, Table 9a and 9b.

8.0 Regulatory Decision

Health Canada's PMRA, under the authority of the *Pest Control Products Act* and Regulations, has granted conditional registration for the sale and use of Tea Tree Oil Technical and Timorex Gold, containing the technical grade active ingredient tea tree oil, to control powdery mildew on greenhouse pepper, tomato and cucumber, suppress powdery mildew on grape, strawberry and cucurbit vegetables, suppress downy mildew on grape and greenhouse cucumber, and suppress late blight on greenhouse tomato.

An evaluation of available scientific information found that, under the approved conditions of use, the product has value and does not present an unacceptable risk to human health or the environment.

Although the risks and value have been found acceptable when all risk-reduction measures are followed, as a condition of these registrations, additional scientific information is being requested from the applican. For more details, refer to the Section 12 Notice associated with these conditional registrations. The applicant will be required to submit this information within the time frames indicated below.

NOTE: The PMRA will publish a consultation document at the time when there is a proposed decision on applications to convert these conditional registrations to full registrations or on applications to renew the conditional registrations, whichever occurs first.

Human Health

- All published and unpublished studies of the developmental toxicity of tea tree oil must be submitted by 1 September 2015.

- Information to characterize the metabolic pathways of the major components of tea tree oil and whether residues of the major components and their metabolites are present on treated crops after the application of Timorex Gold must be submitted by 1 September 2015.

List of Abbreviations

µL	microlitre
a.i.	active ingredient
bw	body weight
CAS	Chemical Abstracts Service
CGPD	Canadian Grower Priority Database
cm	centimetre
EC_{50}	effective concentration on 50% of the population
EDE	estimated dietary exposure
EEC	estimated environmental concentration
F_{int}	harmonized foliar deposition fraction
FIR	food ingestion rate
FRAC	Fungicide Resistance Action Committee
g	gram
GC	gas chromatography
ha	hectare
HDPE	high-density polyethylene
hr	hour
IUPAC	International Union of Pure and Applied Chemistry
kg	kilogram
K_{ow}	*n*–octanol-water partition coefficient
L	litre
LC_{50}	lethal concentration 50%
LD_{50}	lethal dose 50%
LOAEL	lowest observed adverse effect level
LOC	level of concern
LOQ	limit of quantitation
LR_{50}	lethal rate 50%
mg	milligram
mL	millilitre
MAS	maximum average score
MMAD	mass median aerodynamic diametre
MIS	maximum irritation score
MRL	maximum residue limit
MS	mass spectrometry
MSHA	Mine Safety and Health Administration
NCE	normochromatic erythrocytes
NIOSH	National Institute for Occupational Safety and Health
nm	nanometre
NOAEL	no observed adverse effect level
Pa	pascal
PCPA	Pest Control Product Act
p*K*a	dissociation constant
PLE	polychromatic erythrocytes
PMRA	Pest Management Regulatory Agency
REI	restricted-entry interval

RQ	risk quotient
SI	stimulation index
SPF	specific pathogen
TGAI	technical grade active ingredient
TSMP	Toxic Substances Management Policy
US	United States
UV	ultraviolet

Appendix I Tables and Figures

Table 1 Summary of Acute Toxicity, Irritative Effects, Sensitization, and Mutagenticity for Timorex Gold Containing Tea Tree Oil

STUDY	SPECIES/STRAIN AND DOSES	RESULT	TARGET ORGAN/SIGNIFICANT EFFECTS/COMMENTS	REFERENCE
Acute oral toxicity Exposure by gavage	Rat – Sprague-Dawley (5 ♀) 2000 mg/kg bw, limit test	LD_{50} > 2000 mg/kg bw **Low acute toxicity**	No mortality occurred	1745062
Acute dermal toxicity Semi-occlusive exposure, 24 hr	Rat- Sprague-Dawley (5/sex) 2000 mg/kg bw, limit test	LD_{50} > 2000 mg/kg bw (♂ + ♀) **Low acute toxicity**	No mortality occurred	1745063
Acute inhalation toxicity Nose-only exposure chamber	Rat – Wistar (SPF)[a] (5/sex/group) 2.2, 3.1, 5.2 mg/L[b]; MMAD[c]: 1.86–1.87, 1.90–2.18, 1.70–2.14 µm	LC_{50} > 5.2 mg/L (♀), > 3.1 mg/L (♂), < 5.2 mg/L (♂ + ♀) **Low acute toxicity**	Three males and one female exposed to 5.2 mg/L died during the study Decreased spontaneous activity, hunched posture, ruffled fur, tachypnea reported in rats at all concentrations tested	1745065
Eye irritation	Rabbit – New Zealand White (3 ♂) 0.1 mL/eye (unrinsed)	MAS = 35.7[d] **Moderately irritating**	Corneal opacity (3/3) and iritis (3/3) with resolution by day 14	1745066
Eye irritation	Rabbit – New Zealand White (6 ♀) 0.1 mL/eye in rinsed and unrinsed eyes	Unrinsed eyes MAS = 32.8 Rinsed eyes MAS = 8.9 **Moderately irritating**	Unrinsed eyes Corneal opacity, iritis, conjunctival redness, chemosis, and discharge cleared by day 14 Rinsed eyes Similar findings, but cleared by day 7	1967998

STUDY	SPECIES/STRAIN AND DOSES	RESULT	TARGET ORGAN/SIGNIFICANT EFFECTS/COMMENTS	REFERENCE
Dermal irritation Semi-occluded exposure, 4 hr	Rabbit- New Zealand White (2 ♂, 1 ♀) 0.5 mL applied to intact skin	MAS = 2.6 **Mildly irritating**	Well-defined erythema (3/3) at 72 hr increasing to moderate (1/3) at 4–5 days; Very slight edema (3/3) at 72 hr	1745067
Dermal irritation Semi-occluded exposure, 4 hr	Rabbit – New Zealand White (3 ♀) 0.5 mL applied to intact skin	MAS = 4.4 **Moderately irritating**	Well-defined erythema and slight edema (3/3) at 24 hr; Moderate to severe erythema (2/3), well-defined erythema (1/3), and slight edema (3/3) at 48 and 72 hr	1967999
Dermal sensitization Local lymph node assay	Mice (5 ♀/goup) 25 µL of 25, 50, 100% Timorex Gold topically applied to ears of mice for 3 days	SI = 2.4, 5.2, 6.2 for the 25, 50 and 100% Timorex Gold groups, respectively[e] **Positive sensitizer**		1745068

[a] SPF = specific pathogen free
[b] Values reported are gravimetric concentrations
[c] MMAD = mass median aerodynamic diameter
[d] MAS = maximum average score (i.e., 24, 48, 72 hr)
[e] SI = stimulation index

Table 2 Summary of Acute Toxicity, Irritative Effects, Sensitization, Short-term Toxicity, Developmental Toxicity, and Mutagenicity Information for Tea Tree Oil

STUDY	SPECIES/STRAIN AND DOSES	RESULT	TARGET ORGAN / SIGNIFICANT EFFECTS / COMMENTS	REFERENCE
Acute oral toxicity Exposure by gavage	Rat – Sprague Dawley SPF[a] and non-SPF (5/sex/group) SPF: 2.5, 2.6, 2.75, 3 mL/kg bw, non-SPF: 1.70, 2.10, 2.15, 2.25, 2.4 mL/kg bw	LD_{50} (♂ + ♀) SPF = 2393–2450 mg/kg bw, non-SPF = 1752–1794 mg/kg bw **Low acute toxicity**	Weeping eyes, bloodied noses, lack of tonus in forelimbs	1745015
Acute dermal toxicity	Rabbit – New Zealand White (5/sex) 2000 mg/kg bw, limit test	LD_{50} (♂ + ♀) > 2000 mg/kg bw **Low acute toxicity**	No mortalities occurred	1745015
Acute inhalation toxicity Nose-only exposure chamber	Rat – Wistar (HsdCpb: WU) (5/sex/group) 0, 0.77, 3.69, 5.06 mg/L; mean particle size: 1.60–0.74 µm	LC_{50} (♂ + ♀) = 3.64 mg/L **Low acute toxicity**	Lethargy, dullness, nasal discharge, tremors, ataxia, urine soaked perineum, dyspnea, slight salivation, and recumbency in treated rats. One rat that died during the study had lung congestion	2102381
Eye irritation Chorioallanto ic membrane vascular assay Non-guideline study supplementar y study	Chicken egg – Fertile White Leghorn; (6 eggs per test material, 2 eggs for negative control, 4 eggs for positive control) Main camp tea tree oil, 0.1 g test material/egg	**Severely irritating** Accepted as a supplementary study		1745016

STUDY	SPECIES/STRAIN AND DOSES	RESULT	TARGET ORGAN / SIGNIFICANT EFFECTS / COMMENTS	REFERENCE
Primary dermal irritation	Rabbit – New Zealand White (6 animals, sex not specified) (intact and abraded skin) 0.5 mL/rabbit	MIS = 5.2[b, c] **Severely irritating**	Well defined to severe erythema and barely perceptible to slight edema observed for intact skin sites and increased edema and erosions noted for the treated abraded skin sites.	1745015
30 day Dermal irritation Non-guideline study supplementary study	Rabbit – New Zealand White (6 ♀) 0.5 mL undiluted tea tree oil on day 1; 25% tea tree oil (in paraffin oil) on days 2–5, 8–12, 15–19, and 22–30	**Severely irritating**	Undiluted tea tree oil produced severe irritation on day 1. 25% tea tree oil produced mild hyperplastic dermatitis based on histopathology of terminal skin biopsies.	1745015
Dermal sensitization Guinea pig maximization assay	Guinea pig – Albino (HA strain) (20 animals/group (test and negative control) (sex not specified) 1st intradermal induction (0.1 mL 5% tea tree oil in paraffin oil), 2nd intradermal induction (1:1:1 tea tree oil, saline, Freund's complete adjuvant), epidermal induction: undiluted tea tree oil; challenge: 30% tea tree oil (in petroleum jelly)	**Skin sensitizer**	No positive reactions were observed following challenge in any test or negative control animals, but positive control was not included in the study. Based on published clinical case study results for skin sensitization and the results of skin sensitization testing for Timorex Gold, tea tree oil is considered to be a potential skin sensitizer.	1745015

STUDY	SPECIES/STRAIN AND DOSES	RESULT	TARGET ORGAN / SIGNIFICANT EFFECTS / COMMENTS	REFERENCE
Bacterial reverse mutation assay Plate incorporation test	*Salmonella typhimurium* strains TA 98, TA 100, TA 102 10, 25, 50, 100, and 150 uL of serial two-fold dilutions of 10 mg/mL tea tree oil with and without metabolic activation	Non-mutagenic	No significant increases in revertant colonies for any strain, at doses < 50 ug/plate with or without metabolic activation.	1745015
In vivo mammalian cytogenetics (bone marrow micronuclei)	Mouse – Swiss outbred albio (5/sex/dose/time point) 0, 1000, 1350, or 1750 mg/kg bw tea tree oil in corn oil by gavage Bone marrow cells harvested at 24 and 48 hr	Non-mutagenic	No significant increases in bone marrow micronuclei at any dose level in either sex and at any time point ≥ 1350 mg/kg: wobbly gate at 24 hr; 1750 mg/kg: labored breathing at 24 hr, rough coat at 48 hr Cytotoxicity observed at the highest dose at 48 hr in both sexes (significant decrease in PCE/(PCE + NCE) ratio)[d]	1745022
Short-term oral toxicity 90 day rodent	Rat – Wistar (10/sex/dose group) 0, 30, 60, 120 mg/kg bw/day in peanut oil 30 rats/sex/dose in the high dose group. 10 rats/sex sacrificed at 14 and 28 days post dosing to assess reversibility of effects	NOAEL = ♂ 30 mg/kg bw/day; ♀ 60 mg/kg bw/day LOAEL = ♂ 60 mg/kg bw/day; ♀ 120 mg/kg bw/day	60 mg/kg bw/day: ♂ ↓ sperm counts/motility; cell debris in epididymal lumen (1 rat) ♀ ↑ relative liver weights (no histo- or gross pathological lesions) 120 mg/kg bw/day: ♂ flaccid testes at end of treatment and after 14 and 28 day recovery period; ↓ epididymal and testes weights/organ to body wt ratios in 28 day recovery group; degenerative changes in seminiferous tubules, sperm granulomas, cellular debris in lumen of epididymis with similar or	2102382

STUDY	SPECIES/STRAIN AND DOSES	RESULT	TARGET ORGAN / SIGNIFICANT EFFECTS / COMMENTS	REFERENCE
			increased incidences in recovery groups ♀ 2 moribund rats sacrificed at 40 and 41 days; ↑ relative liver weights (no dose-response or histo- or gross pathological lesions)	
Developmental toxicity - oral	Rat – Wistar (14–25 ♀/dose group) 0, 30, 60, 125, 250 mg/kg bw/day α-terpinene on gestation days 6–15 (purity 89%)	Maternal NOAEL = 60 mg/kg bw/day LOAEL = 125 mg/kg bw/day Developmental NOAEL = 30 mg/kg bw/day LOAEL = 60 mg/kg bw/day	Maternal 125 mg/kg bw/day and higher: ↓ body weight gain and cumulative body weight gain (adjusted for gravid uterus); 250 mg/kg bw/day: ↓ body weight, decreased pregnancy rate Developmental 60 mg/kg bw/day and higher: ↑ incidences of retarded ossification and irregularly shaped os squamosum; 125 mg/kg bw/day and higher: ↑ incidences of incomplete ossification of supraoccipital bone and/or shorter ribs; 250 mg/kg bw/day: ↓ fetal body weights and absolute thymus weights, ↑ absolute kidney weights, ↑ incidences of extra cervical ribs	2102384

[a] SPF = specific pathogen free
[b] MIS = maximum irritation score
[c] Primary skin irritation study results were classified based on the MIS
[d] PCE = polychromatic erythrocytes; NCE = normochromatic erythrocytes

Table 3 Screening level risk assessment on non-target species

Organism	Test Substance[1]	Toxicity value	Uncertainty Factor	EEC[3]	Units[4]	RQ[5]
Bee[2]	BM 608	LD_{50} >96	1.12	4.48[2]	kg/ha	<0.04
Predatory arthropod	BM 608	LR_{50} >961	1.0	4485	g/ha	<4.7
Parasitic arthropod	BM 608	LR_{50} >240	1.0	4485	g/ha	<19
20 g bird, insectivore (small insect)	BM 608	LD_{50} > 476	0.1	226	mg/kg bw	4.8
100 g bird, insectivore (small insect)	BM 608	LD_{50} > 476	0.1	176	mg/kg bw	3.7
1000 g bird, herbivore (short grass)	BM 608	LD_{50} > 476	0.1	184	mg/kg bw	3.9
15 g mammal, insectivore (small insect)	tea tree oil	LD_{50} 1776	0.1	130	mg/kg bw	0.73
35 g mammal, herbivore (short grass)	tea tree oil	LD_{50} 1776	0.1	407	mg/kg bw	2.3
1000 g mammal, herbivore (short grass)	tea tree oil	LD_{50} 1776	0.1	218	mg/kg bw	1.2
Aquatic invertebrate	BM 608	48hr EC_{50} 0.35	0.5	0.56	mg/L	3.2
Fish	tea tree oil	96hr LC_{50} >100	0.1	0.56	mg/L	<0.06
	BM 608	96hr LC_{50} 1.3	0.1	0.56	mg/L	4.3
Amphibian[6]	tea tree oil	96hr LC_{50} >100	0.1	3.0	mg/L	<0.30
	BM 608	96hr LC_{50} 1.3	0.1	3.0	mg/L	23
Aquatic plant	BM 608	72hr EC_{50} 1.7	0.5	0.56	mg/L	0.66

1 BM 608 formulation contains 23.8% tea tree oil (nominal active ingredient), trade name is Timorex Gold.

2 In the case of bees, the factor of 1.12 is applied to the LD_{50} in µg/bee to convert it to the equivalent rate in kg/ha. The EEC (single application rate of 4.45 kg a.i./ha) is divided by the converted value and compared to the LOC of 0.4 for bees.

3 Estimated environmental concentrations (EEC) are based on 9 applications of 4.45 kg tea tree oil/ha with a minimum interval of 7 days between applications. A dissipation half-life of 1 day was assumed between applications for both terrestrial and aquatic assessments (based on >50% of the initial measured residues declining within one day in a crop residue study, PMRA-1745081; the dissipation is attributed to rapid volatilization which is also expected in the aquatic environment). This cumulative application rate is used for arthropods, and the resulting RQ (exposure/toxicity) is compared to an LOC of 2.
For birds and mammals, estimated dietary exposure (EDE) is calculated from the EEC using the following formula: (FIR/BW) x EEC, where:
FIR: Food Ingestion Rate. For generic birds with body weight less than or equal to 200 g, the "passerine" equation was used; for generic birds with body weight greater than 200 g, the "all birds" equation was used:
Passerine Equation (body weight < or = 200 g): FIR (g dry weight/day) = $0.398(\text{BW in g})^{0.850}$
All birds Equation (body weight > 200 g): FIR (g dry weight/day) = $0.648(\text{BW in g})^{0.651}$.
For mammals, the "all mammals" equation was used: FIR (g dry weight/day) = $0.235(\text{BW in g})^{0.822}$
BW: Generic Body Weight
EEC: Concentration of pesticide on food item. At the screening level, relevant food items representing the most conservative EEC for each feeding guild are used.
The aquatic EEC values are based on a water depth of 15 cm to represent a seasonal water body for amphibians and 80 cm to represent a permanent water body for the remaining aquatic organisms.

4 All units are on the basis of the active ingredient, tea tree oil.

5 Risk quotient (RQ) = EEC / (Endpoint × Uncertainty factor); shaded cells indicate that the screening level RQ exceeds the LOC. The screening level LOC values are 2.0 for predatory and parasitic arthropods, 0.4 for bees, and 1.0 for the remaining organisms.

6 Amphibian assessment is based on fish toxicity data.

Table 4 Further Characterization of Acute Risk to Non-Target Arthropod, Bird (Maximum Residues), and Mammal (Maximum Residues) Species: In-Field Exposure

Organism	Substance[1]	Toxicity value	Uncertainty Factor	EEC[2]	Units[3]	RQ[4]
Predatory arthropod	BM 608	LR50 >961	1.0	3588	g/ha	<3.73
Parasitic arthropod	BM 608	LR50 >240	1.0	3588	g/ha	<15
20g bird: small insects	BM 608	LD_{50} > 476	0.1	226	mg/kg bw	4.8
20g bird: grain, seeds	BM 608	LD_{50} > 476	0.1	57	mg/kg bw	1.2
20g bird: fruit	BM 608	LD_{50} > 476	0.1	113	mg/kg bw	2.4
100g bird: small insects	BM 608	LD_{50} > 476	0.1	176	mg/kg bw	3.7
100g bird: large insects	BM 608	LD_{50} > 476	0.1	44	mg/kg bw	0.9
100g bird: fruit	BM 608	LD_{50} > 476	0.1	88	mg/kg bw	1.9
100 g bird: grain and seed	BM 608	LD_{50} > 476	0.1	44	mg/kg bw	0.9
1000g bird: small insects	BM 608	LD_{50} > 476	0.1	52	mg/kg bw	1.1
1000g bird: large insects	BM 608	LD_{50} > 476	0.1	13	mg/kg bw	0.3
1000g bird: grain, seeds	BM 608	LD_{50} > 476	0.1	13	mg/kg bw	0.3
1000g bird: frugivore	BM 608	LD_{50} > 476	0.1	26	mg/kg bw	0.5
1000g bird: short grass	BM 608	LD_{50} > 476	0.1	184	mg/kg bw	3.9
1000g bird: forage crops	BM 608	LD_{50} > 476	0.1	170	mg/kg bw	3.6
1000g bird: long grass	BM 608	LD_{50} > 476	0.1	112	mg/kg bw	2.4
35 g mammal: small insects	tea tree oil	LD_{50} 1776	0.1	114	mg/kg bw	0.6
35 g mammal: large insects	tea tree oil	LD_{50} 1776	0.1	29	mg/kg bw	0.2
35 g mammal: grain, seeds	tea tree oil	LD_{50} 1776	0.1	29	mg/kg bw	0.2
35 g mammal: frugivore	tea tree oil	LD_{50} 1776	0.1	57	mg/kg bw	0.3
35g mammal: short grass	tea tree oil	LD_{50} 1776	0.1	407	mg/kg bw	2.3
35g mammal: forage crops	tea tree oil	LD_{50} 1776	0.1	377	mg/kg bw	2.1
35g mammal: long grass	tea tree oil	LD_{50} 1776	0.1	249	mg/kg bw	1.4
1000g mammal: small insects	tea tree oil	LD_{50} 1776	0.1	61	mg/kg bw	0.3
1000g mammal: large insects	tea tree oil	LD_{50} 1776	0.1	15	mg/kg bw	0.1
1000 g mammal: grain, seeds	tea tree oil	LD_{50} 1776	0.1	15	mg/kg bw	0.1
1000 g mammal: frugivore	tea tree oil	LD_{50} 1776	0.1	30	mg/kg bw	0.2
1000g mammal: short grass	tea tree oil	LD_{50} 1776	0.1	218	mg/kg bw	1.2
1000g mammal: forage crops	tea tree oil	LD_{50} 1776	0.1	201	mg/kg bw	1.1
1000g mammal: long grass	tea tree oil	LD_{50} 1776	0.1	133	mg/kg bw	0.7

1 BM 608 formulation contains 23.8% tea tree oil (nominal active ingredient), trade name is Timorex Gold.

2 In-field estimated environmental concentrations (EEC) are based on 9 applications of 4.45 kg tea tree oil/ha with a minimum interval of 7 days between applications. A dissipation half-life of 1 day was assumed between applications for both terrestrial and aquatic assessments (based on >50% of the initial measured residues declining within one day in a crop residue study, PMRA-1745081; the dissipation is attributed to rapid volatilization which is also expected in the aquatic environment). For arthropods, the cumulative application rate was multiplied by the foliar deposition fraction (Fint) of 0.8 for grapes.
For birds and mammals, estimated dietary exposure (EDE) is calculated from the EEC using the following formula: (FIR/BW) x EEC, where:
FIR: Food Ingestion Rate.
For mammals, the "all mammals" equation was used: FIR (g dry weight/day) = $0.235(\text{BW in g})^{0.822}$
BW: Generic Body Weight
EEC: Concentration of pesticide on food item Maximum residues values were used.

3 All units are on the basis of the active ingredient, tea tree oil.

4 Risk quotient (RQ) = EEC / (Endpoint × Uncertainty factor); shaded cells indicate that the refined RQ exceeds the LOC. The LOC values for refined assessments are 1.0 for all organisms.

Table 5 Further Characterization of Acute Risk to Non-Target Arthropods, Bird (Maximum Residues) and Mammal (Maximum Residues) Species: Off-Field Exposure

Organism	Substance[1]	Toxicity value	Uncertainty Factor	EEC[2]	Units[3]	RQ[4]
Predatory arthropod	BM 608	LR_{50} >961	1.0	332	g/ha	<0.4
Parasitic arthropod	BM 608	LR_{50} >240	1.0	332	g/ha	<1.4
20g bird: small insects	BM 608	LD_{50} > 476	0.1	167	mg/kg bw	3.5
20g bird: grain, seeds	BM 608	LD_{50} > 476	0.1	42	mg/kg bw	0.9
20g bird: fruit	BM 608	LD_{50} > 476	0.1	84	mg/kg bw	1.8
100g bird: small insects	BM 608	LD_{50} > 476	0.1	131	mg/kg bw	2.7
100g bird: large insects	BM 608	LD_{50} > 476	0.1	33	mg/kg bw	0.7
100g bird: fruit	BM 608	LD_{50} > 476	0.1	65	mg/kg bw	1.4
100 g bird: grain and seed	BM 608	LD_{50} > 476	0.1	33	mg/kg bw	0.7
1000g bird: small insects	BM 608	LD_{50} > 476	0.1	38	mg/kg bw	0.8
1000g bird: large insects	BM 608	LD_{50} > 476	0.1	10	mg/kg bw	0.2
1000g bird: grain, seeds	BM 608	LD_{50} > 476	0.1	10	mg/kg bw	0.2
1000g bird: frugivore	BM 608	LD_{50} > 476	0.1	19	mg/kg bw	0.4
1000g bird: short grass	BM 608	LD_{50} > 476	0.1	136	mg/kg bw	2.9
1000g bird: forage crops	BM 608	LD_{50} > 476	0.1	126	mg/kg bw	2.7
1000g bird: long grass	BM 608	LD_{50} > 476	0.1	83	mg/kg bw	1.8
35 g mammal: small insects	tea tree oil	LD_{50} 1776	0.1	84	mg/kg bw	0.5
35 g mammal: large insects	tea tree oil	LD_{50} 1776	0.1	21	mg/kg bw	0.1
35 g mammal: grain, seeds	tea tree oil	LD_{50} 1776	0.1	21	mg/kg bw	0.1
35 g mammal: frugivore	tea tree oil	LD_{50} 1776	0.1	42	mg/kg bw	0.2
35g mammal: short grass	tea tree oil	LD_{50} 1776	0.1	301	mg/kg bw	1.7
35g mammal: forage crops	tea tree oil	LD_{50} 1776	0.1	279	mg/kg bw	1.6
35g mammal: long grass	tea tree oil	LD_{50} 1776	0.1	184	mg/kg bw	1.0
1000g mammal: small insects	tea tree oil	LD_{50} 1776	0.1	45	mg/kg bw	0.3
1000g mammal: large insects	tea tree oil	LD_{50} 1776	0.1	11	mg/kg bw	0.1
1000 g mammal: grain, seeds	tea tree oil	LD_{50} 1776	0.1	11	mg/kg bw	0.1
1000 g mammal: frugivore	tea tree oil	LD_{50} 1776	0.1	23	mg/kg bw	0.1
1000g mammal: short grass	tea tree oil	LD_{50} 1776	0.1	161	mg/kg bw	0.9
1000g mammal: forage crops	tea tree oil	LD_{50} 1776	0.1	149	mg/kg bw	0.8
1000g mammal: long grass	tea tree oil	LD_{50} 1776	0.1	98	mg/kg bw	0.6

[1] BM 608 formulation contains 23.8% tea tree oil (nominal active ingredient), trade name is Timorex Gold.

[2] Off-field estimated environmental concentrations (EEC) for birds and mammals are based on 74% of spray drift from 9 early airblast applications of 4.45 kg tea tree oil/ha with a minimum interval of 7 days between applications. A dissipation half-life of 1 day was assumed between applications for both terrestrial and aquatic assessments (based on >50% of the initial measured residues declining within one day in a crop residue study, PMRA-1745081; the dissipation is attributed to rapid volatilization which is also expected in the aquatic environment).
For arthropods, the cumulative application rate was multipled by the foliar deposition fraction (Fint) of 0.8 for grapes.
For birds and mammals, estimated dietary exposure (EDE) is calculated from the EEC using the following formula: (FIR/BW) x EEC, where:
FIR: Food Ingestion Rate.
For mammals, the "all mammals" equation was used: FIR (g dry weight/day) = $0.235(\text{BW in g})^{0.822}$
BW: Generic Body Weight
EEC: Concentration of pesticide on food item. Maximum residues values were used.

[3] All units are on the basis of the active ingredient, tea tree oil.

[4] Risk quotient (RQ) = EEC / (Endpoint × Uncertainty factor); shaded cells indicate that the refined RQ exceeds the LOC. The LOC values for refined assessments are 1.0 for all organisms.

Table 6 Further Characterization of Risk Of Acute Toxicity Non-Target Bird and Mammal Species: Mean Residues and On-Field Exposure

Organism	Substance[1]	Toxicity value	Uncertainty Factor	EEC[2]	Units[3]	RQ[4]
20g bird: small insects	BM 608	LD_{50} > 476	0.1	126	mg/kg bw	2.6
20g bird: grain, seeds	BM 608	LD_{50} > 476	0.1	27	mg/kg bw	0.6
20g bird: fruit	BM 608	LD_{50} > 476	0.1	54	mg/kg bw	1.1
100g bird: small insects	BM 608	LD_{50} > 476	0.1	98	mg/kg bw	2.1
100g bird: large insects	BM 608	LD_{50} > 476	0.1	21	mg/kg bw	0.4
100g bird: fruit	BM 608	LD_{50} > 476	0.1	42	mg/kg bw	0.9
100 g bird: grain and seed	BM 608	LD_{50} > 476	0.1	21	mg/kg bw	0.4
1000g bird: small insects	BM 608	LD_{50} > 476	0.1	29	mg/kg bw	0.6
1000g bird: large insects	BM 608	LD_{50} > 476	0.1	6.1	mg/kg bw	0.1
1000g bird: grain, seeds	BM 608	LD_{50} > 476	0.1	6.1	mg/kg bw	0.1
1000g bird: frugivore	BM 608	LD_{50} > 476	0.1	12	mg/kg bw	0.3
1000g bird: short grass	BM 608	LD_{50} > 476	0.1	65	mg/kg bw	1.4
1000g bird: forage crops	BM 608	LD_{50} > 476	0.1	56	mg/kg bw	1.2
1000g bird: long grass	BM 608	LD_{50} > 476	0.1	37	mg/kg bw	0.8
35g mammal: small insects	tea tree oil	LD_{50} 1776	0.1	64	mg/kg bw	0.4
35g mammal: large insects	tea tree oil	LD_{50} 1776	0.1	14	mg/kg bw	0.1
35g mammal: grain, seeds	tea tree oil	LD_{50} 1776	0.1	14	mg/kg bw	0.1
35g mammal: frugivore	tea tree oil	LD_{50} 1776	0.1	27	mg/kg bw	0.2
35g mammal: short grass	tea tree oil	LD_{50} 1776	0.1	145	mg/kg bw	0.81
35g mammal: forage crops	tea tree oil	LD_{50} 1776	0.1	125	mg/kg bw	0.70
35g mammal: long grass	tea tree oil	LD_{50} 1776	0.1	81	mg/kg bw	0.46
1000g mammal: small insects	tea tree oil	LD_{50} 1776	0.1	34	mg/kg bw	0.2
1000g mammal: large insects	tea tree oil	LD_{50} 1776	0.1	7.3	mg/kg bw	0.04
1000g mammal: grain, seeds	tea tree oil	LD_{50} 1776	0.1	7.3	mg/kg bw	0.04
1000g mammal: frugivore	tea tree oil	LD_{50} 1776	0.1	15	mg/kg bw	0.1
1000g mammal: short grass	tea tree oil	LD_{50} 1776	0.1	77	mg/kg bw	0.43
1000g mammal: forage crops	tea tree oil	LD_{50} 1776	0.1	67	mg/kg bw	0.37
1000g mammal: long grass	tea tree oil	LD_{50} 1776	0.1	43	mg/kg bw	0.24

1 BM 608 formulation contains 23.8% tea tree oil (nominal active ingredient), trade name is Timorex Gold.

2 On-field estimated environmental concentrations (EEC) are based on 9 applications of 4.45 kg tea tree oil/ha with a minimum interval of 7 days between applications. A dissipation half-life of 1 day was assumed between applications for both terrestrial and aquatic assessments (based on >50% of the initial measured residues declining within one day in a crop residue study, PMRA-1745081; the dissipation is attributed to rapid volatilization which is also expected in the aquatic environment).
For birds and mammals, estimated dietary exposure (EDE) is calculated from the EEC using the following formula: (FIR/BW) x EEC, where:
FIR: Food Ingestion Rate.
For mammals, the "all mammals" equation was used: FIR (g dry weight/day) = $0.235(\text{BW in g})^{0.822}$
BW: Generic Body Weight
EEC: Concentration of pesticide on food item. Maximum residues values were used.

3 All units are on the basis of the active ingredient, tea tree oil.

4 Risk quotient (RQ) = EEC / (Endpoint × Uncertainty factor); shaded cells indicate that the refined RQ exceeds the LOC. The LOC values for refined assessments are 1.0 for all organisms.

Table 7 Further Characterisation of Risk of Acute Toxicity to Non-Target Bird and Mammal Species: Mean Residues and Off-Field Exposure

Organism	Substance[1]	Toxicity value	Uncertainty Factor	EEC[2]	Units[3]	RQ[4]
20g bird: small insects	BM 608	LD_{50} > 476	0.1	93	mg/kg bw	2.0
20g bird: grain, seeds	BM 608	LD_{50} > 476	0.1	20	mg/kg bw	0.4
20g bird: fruit	BM 608	LD_{50} > 476	0.1	40	mg/kg bw	0.8
100g bird: small insects	BM 608	LD_{50} > 476	0.1	73	mg/kg bw	1.5
100g bird: large insects	BM 608	LD_{50} > 476	0.1	16	mg/kg bw	0.3
100g bird: grains, seeds	BM 608	LD_{50} > 476	0.1	16	mg/kg bw	0.3
100g bird: fruit	BM 608	LD_{50} > 476	0.1	31	mg/kg bw	0.7
1000g bird: small insects	BM 608	LD_{50} > 476	0.1	21	mg/kg bw	0.4
1000g bird: large insects	BM 608	LD_{50} > 476	0.1	4.5	mg/kg bw	0.1
1000g bird: grains, seeds	BM 608	LD_{50} > 476	0.1	4.5	mg/kg bw	0.1
1000g bird: fruit	BM 608	LD_{50} > 476	0.1	9.1	mg/kg bw	0.2
1000g bird: short grass	BM 608	LD_{50} > 476	0.1	48	mg/kg bw	1.0
1000g bird: forage crops	BM 608	LD_{50} > 476	0.1	42	mg/kg bw	0.9
1000g bird: long grass	BM 608	LD_{50} > 476	0.1	27	mg/kg bw	0.6
35g mammal: small insects	tea tree oil	LD_{50} > 476	0.1	47	mg/kg bw	0.3
35g mammal: large insects	tea tree oil	LD_{50} > 476	0.1	10	mg/kg bw	0.1
35g mammal: grains, seeds	tea tree oil	LD_{50} > 476	0.1	10	mg/kg bw	0.1
35g mammal: fruit	tea tree oil	LD_{50} > 476	0.1	20	mg/kg bw	0.1
35g mammal: short grass	tea tree oil	LD_{50} 1776	0.1	107	mg/kg bw	0.6
35g mammal: forage crops	tea tree oil	LD_{50} 1776	0.1	92	mg/kg bw	0.5
35g mammal: long grass	tea tree oil	LD_{50} 1776	0.1	60	mg/kg bw	0.3
1000g mammal: small insects	tea tree oil	LD_{50} > 476	0.1	25	mg/kg bw	0.1
1000g mammal: large insects	tea tree oil	LD_{50} > 476	0.1	5.4	mg/kg bw	0.0
1000g mammal: grains, seeds	tea tree oil	LD_{50} > 476	0.1	5.4	mg/kg bw	0.0
1000g mammal: fruit	tea tree oil	LD_{50} > 476	0.1	11	mg/kg bw	0.1
1000g mammal: short grass	tea tree oil	LD_{50} 1776	0.1	57	mg/kg bw	0.3
1000g mammal: forage crops	tea tree oil	LD_{50} 1776	0.1	49	mg/kg bw	0.3
1000g mammal: long grass	tea tree oil	LD_{50} 1776	0.1	32	mg/kg bw	0.2

[1] BM 608 formulation contains 23.8% tea tree oil (nominal active ingredient), trade name is Timorex Gold.

[2] Off-field estimated environmental concentrations (EEC) for birds and mammals are based on 74% of spray drift from 9 early airblast applications of 4.45 kg tea tree oil/ha with a minimum interval of 7 days between applications. A dissipation half-life of 1 day was assumed between applications for both terrestrial and aquatic assessments (based on >50% of the initial measured residues declining within one day in a crop residue study, PMRA-1745081; the dissipation is attributed to rapid volatilization which is also expected in the aquatic environment). For birds and mammals, estimated dietary exposure (EDE) is calculated from the EEC using the following formula: (FIR/BW) x EEC, where:
FIR: Food Ingestion Rate.
For mammals, the "all mammals" equation was used: FIR (g dry weight/day) = $0.235(\text{BW in g})^{0.822}$
BW: Generic Body Weight
EEC: Concentration of pesticide on food item. Maximum residues values were used.

[3] All units are on the basis of the active ingredient, tea tree oil.

[4] Risk quotient (RQ) = EEC / (Endpoint × Uncertainty factor); shaded cells indicate that the refined RQ exceeds the LOC. The LOC values for refined assessments are 1.0 for all organisms.

Table 8 Alternative Active Ingredients Registered for Control/Suppression of Claimed Diseases on the Timorex Gold Accepted Label

Crop	Disease	Active Ingredient and FRAC Fungicide Group	
		Conventional	Non-conventional
Greenhouse tomato	Powdery mildew	Boscalid (7) + pyraclostrobin (11) (suppression)	Garlic (NC) (suppression) Potassium bicarbonate (NC) *Streptomyces lydicus* (NC) Sulphur (M2)
	Late blight	Ametoctradin (45) Ametoctradin (45) + dimethomorph (40) Captan (M4) Chlorothalonil (M5) Copper (M1) Dimethomorph (40) Maneb (M3) Pyraclostrobin (11) (all for field use)	Garlic (NC) (may inhibit symptoms) Phosphonates (33) (field use, suppression)
Greenhouse pepper	Powdery mildew	Boscalid (7) + pyraclostrobin (11)	*Bacillus subtilis* (44) (suppression) Potassium bicarbonate (NC) *Streptomyces lydicus* (NC) Sulphur (M2)
Greenhouse cucumber	Powdery mildew	Boscalid (7) + pyraclostrobin (11) (suppression) Chlorothalonil (M5) (field use) Difenoconazole (3) (field use) Maneb (M3) (field use, suppression) Penthiopyrad (7) (field use) Trifloxystrobin (11) (field use)	*Bacillus subtilis* (44) (suppression) Garlic (NC) (suppression) Potassium bicarbonate (NC) *Reynoutria sachalinensis* (NC) (suppression) *Streptomyces lydicus* (NC)
	Downy mildew	Ametoctradin (45) (field use) Ametoctradin (45) + Dimethomorph (40) (field use) Copper (M1) (field use) Dimethomorph (40) (field use, suppression) Maneb (M3) (field use)	Garlic (NC) (may inhibit symptoms) Phosphonates (33) (field use, suppression)
Cucurbit vegetables	Powdery mildew	Difenoconazole (3) Maneb (M3) (suppression) Penthiopyrad (7) Pyraclostrobin (11) Trifloxystrobin (11)	*Bacillus subtilis* (44) Potassium bicarbonate (NC) *Reynoutria sachalinensis* (NC) (suppression) *Streptomyces lydicus* (NC)
Grape	Powdery mildew	Boscalid (7) Boscalid (7) + pyraclostrobin (11) Difenoconazole (3)	*Bacillus subtilis* (44) Potassium bicarbonate (NC) *Reynoutria sachalinensis* (NC)

Crop	Disease	Active Ingredient and FRAC Fungicide Group	
		Conventional	Non-conventional
		Metrafenone (U8) Quinoxyfen (13) Trifloxystrobin (11)	(suppression) *Streptomyces lydicus* (NC) Sulphur (M2)
	Downy mildew	Boscalid (7) + pyraclostrobin (11) Captan (M4) Copper (M1)	Phosphonates (33)
Strawberry	Powdery mildew	Boscalid (7) + pyraclostrobin (11) Fluopyram (7) Fluopyram (7) + pyrimethanil (9) Quinoxyfen (13) Trifloxystrobin (11)	*Reynoutria sachalinensis* (NC) (suppression) *Streptomyces lydicus* (NC)

Table 9a Use (Label) Claims Proposed by Applicant and Accepted

Proposed Claim	Accepted Claim
1) Control of powdery mildew (*Oidium neolycopersici, O. lycopersici* or *Leveillula taurica*) on greenhouse tomato at the rates of 0.4–0.6%.	Accepted at the rates of 0.5–1.0%.
2) Control of late blight (*Phytophthora infestans*) on greenhouse tomato at the rates of 0.4–0.6%.	Accepted as suppression, rather than control at the rates of 0.5–1.0%.
3) Control of powdery mildew (*Leveillula taurica*) on greenhouse pepper at the rates of 0.4–0.6%.	Accepted at the rates of 0.5–1.0%.
4) Control of powdery mildew (*Sphaerotheca fuliginea* or *Erysiphe cichoracearum*) on greenhouse cucumber at the rates of 0.4–0.8%.	
5) Suppression of downy mildew (*Pseudoperonospora cubensis*) on greenhouse cucumber at the rates of 0.4–0.8%.	
6) Control of powdery mildew (*Uncinula necator*) on grape at the rates of 0.4–0.8%.	Accepted as suppression, rather than control at the rates of 0.5–1.0%.
7) Control of powdery mildew (*Sphaerotheca macularis*) on strawberry at the rates of 0.5–1.0%.	Accepted as suppression, rather than control.

Table 9b Use (Label) Claims Proposed by Applicant and Accepted With Conditions

Proposed Claim	Accepted Claims with Conditions
1) Suppression of powdery mildew (*Sphaerotheca fuliginea* or *Erysiphe cichoracearum*) on cucurbit vegetables crop group at the rates of 0.4–0.8%.	Accepted at the rates of 0.5–1.0%, pending confirmatory value evidence under Canadian growing conditions.
2) Suppression of downy mildew (*Plasmopara viticola*) on grape at the rates of 0.4–0.8%.	

References

A. List of Studies/Information Submitted by Registrant

1.0 Chemistry

PMRA Document Number	Reference
Technical Grade Active Ingredient	
1745011	2009, EPA Transmittal Documents, DACO: 2.16 (EPA) CBI
1745012	2009, Product Chemistry for Tea Tree Oil Technical, DACO: 2.11.1, 2.11.2, 2.11.3, 2.12.1, 2.12.2,2.13.1,2.13.2,2.13.3,2.14.1,2.14.10,2.14.11,2.14.12,2.14.13,2.14.14,2.14.2,2.14.3,2.14.4,2.14.5,2.14.6,2.14.7,2.14.8,2.14.9,2.3.1,2.4,2.5,2.6,2.7,2.8,2.9,3.3.1,3.3.2,3.4.1,3.4.2,3.5.1,3.5.10,3.5.11,3.5.12,3.5.13,3.5.14,3.5.15,3.5.2,3.5.3,3.5.6,3.5.7,3.5.8,3.5.9,8.2.3.2,830.1700,830.1750,830.1800,830.6302,830.6303,830.6304,830.6313,830.6314,830.6315,830.6316,830.6317,830.6319,830.6320,830.6321,830.7000,830.7050,830.7100,830.7200,830.7220,830.7300,830.7370,830.7550,830.7560 CBI
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1745031	2008, Document M, Annex II for the Inclusion of the Active Substance Tea Tree Oil (*Melaleuca alternifolia*) into Annex 1 of the Directive 91/414/EEC, DACO: 12.7, Document M CBI
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1814718	2007, Phys/Chem Testing of Tea Tree Oil, Technical and Terpine-4-ol, Additional 2.14 data, DACO: 2.16 CBI
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1814720	2005, 284004_BIOMOR_191-002., DACO: 2.16 CBI
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PMRA Document Number	Reference
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1814725	2005, 284004_BIOMOR_191-006, DACO: 2.16 CBI
1814726	2005, 284004_BIOMOR_191-008, DACO: 2.16 CBI
1814727	2005, 284004_BIOMOR_191-009, DACO: 2.16 CBI
1814728	2005, 284004_BIOMOR_191-010, DACO: 2.16 CBI
1814729	2005, 284004_BIOMOR_191-011, DACO: 2.16 CBI
1814730	2005, 284004_BIOMOR_191-012, DACO: 2.16 CBI
1814731	1992, Biodegradation and bioaccumulation Data of existing chemicals based on the CSCL Japan, 284004_BIOMOR_192-005, DACO: 2.16 CBI
1814732	1998, Pysiochemical properties of selected monoterpenes, Environment International, Vol. 24, No. 3, pp. 353-358, DACO: 2.16 CBI
1814735	Characterization and aerobic biodegradation of selected monoterpenes, 284004_BIOMOR_792-016, DACO: 2.16 CBI
1814736	2006, EPI suite calculation terpinene-4-ol-3-cyclohexen-1-ol, 4-methyl-1-(1-methylethyl), 284008_BIOMOR_181-002, DACO: 2.16 CBI
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1814740	2006, HSDB search – P-cymene, 284008_BIOMOR_191-014, DACO: 2.16 CBI
1814743	2006, HSDB – Cineole, 284008_BIOMOR_191-015, DACO: 2.16 CBI
1814744	2006, Material Safety Data Sheet – Alpha Terpinene – Tech. 85–90% L-Terpinene, 284008_BIOMOR_953-002, DACO: 2.16 CBI
1814745	2006, Material Safety Data Sheet – Gamma Terpinene, 95% Y-Terpinene, 284008_BIOMOR_953-003, DACO: 2.16 CBI
1814746	2006, Material Safety Data Sheet – Terpinen-4-ol, 97% Terpinen-4-ol, 284008_BIOMOR_953-004, DACO: 2.16 CBI
1814747	2007, Tea Tree Oil Characterization of Tea Tree Oil by UV Spectophotometry, UV ANALYSIS OF TTO 2007-021, DACO: 2.16 CBI

PMRA Document Number	Reference
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End-Use Product	
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1745059	2008, BM 608 Accelerated Storage Stability Study - Physical Tests, DACO: 2.14.13,3.5.10,830.6313 CBI
1745060	2007, Chemical/Physical Testing of BM 608 Formulation, DACO: 2.14.12, 2.14.4, 2.14.5, 2.14.6, 3.5.11, 3.5.6, 3.5.7, 3.5.9, 830.6315, 830.7000, 830.7050, 830.7100, 830.7200, 830.7220, 830.7300 CBI
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1745098	2006, Carson CF, Hammer KA, Riley TV, *Melaleuca alternifolia* (Tea Tree Oil): a Review of Antimicrobial and other medicinal properties, Clinical Microbiology Reviews, pp. 50–62, DACO: 10.2.3.2
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2.0 Human and Animal Health

PMRA Document Number	Reference
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1745015	2009, Acute Toxicity and Genotoxicity Data on Tea Tree Oil, DACO: 4.2.1, 4.2.2, 4.2.5, 4.2.6, 4.5.4, 4.5.7, 4.6.1, 4.6.2, 4.6.5, 4.6.6, 870.1100, 870.1200, 870.2500, 870.2600, 870.5100, 870.5385, M4.5.2
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1745066	2007, Acute Eye Irritation/Corrosion in the Rabbit, DACO: 4.2.4,4.6.4,870.2400
1745067	2007, Acute Dermal irritation/Corrosion in the Rabbit, DACO: 4.2.5,4.6.5,870.2500,M4.5.2
1745068	2007, Skin Sensitization - Local Lymph Node Assay (LLNA), DACO: 4.2.6,4.6.6,870.2600
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1798769	2009, DACO: Clarification_Email
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1814635	2009, Registrants Response to Clarification Request, DACO: 0.8
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2102381	2010, Tea Tree Oil: Acute Inhalation Toxicity Study in Wistar Rats, DACO: 4.2.3,4.6.3,870.1300
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3.0 Environment

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1745075	2009, Toxicity to the Aphid Parasitoid, *Aphidius rhopalosiphi* De Stefani Perez (Hymenoptera, Braconidae) in the Laboratory (Dose Response Test), DACO: 9.2.7(EPA)
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4.0 Value

PMRA Document Number	Reference
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B. Additional Information Considered

i) Published Information

1.0 Human and Animal Health

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ii) Unpublished Information

1.0 Human and Animal Health

PMRA Document Number	Reference
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